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Enhancing the Scope of the Diels–Alder Reaction through Isonitrile Chemistry: Emergence of a New Class of Acyl-Activated Dienophiles

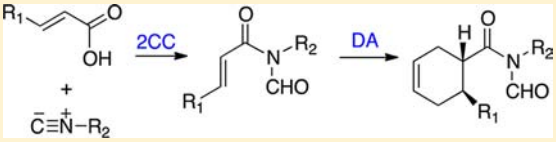
Steven D. Townsend,[†] Xiangyang Wu,[†] and Samuel J. Danishefsky*[,†,‡]

[†]Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10065, United States

[‡]Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027, United States

Supporting Information

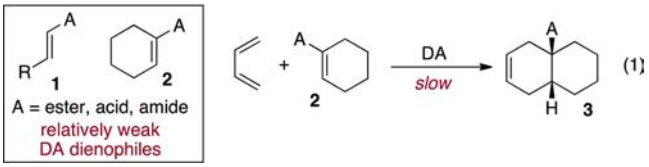
ABSTRACT: α,β-Unsaturated imides, formylated at the nitrogen atom, comprise a new and valuable family of dienophiles for servicing Diels–Alder reactions. These systems are assembled through extension of recently discovered isonitrile chemistry to the domain of α,β-unsaturated acids. Cycloadditions are facilitated by Et_2AlCl, presumably via chelation between the two carbonyl groups of the N-formyl amide. Applications of the isonitrile/Diels–Alder logic to the IMDA reaction, as well as methodologies to modify the N-formyl amide of the resultant cycloaddition product, are described. It is expected that this easily executed chemistry will provide a significant enhancement for application of Diels–Alder reactions to many synthetic targets.



INTRODUCTION

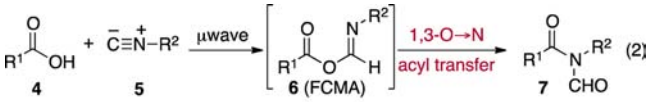
Powerful as the Diels–Alder (DA) reaction is as a resource in chemical synthesis,[1−4] it is certainly not without its limitations. Our laboratory, at various levels over the years, has been involved in addressing some of these limitations in an attempt to raise the overall applicability of DA logic. Our earliest works focused on the synthesis of, then-novel, dienes which would impart to their cycloaddition products easily exploitable, complexity-enhancing access points.[5] More recently, through the use of appropriate dienophiles, we have been able to encompass *trans* junctions within the scope of DA logic.[6,7] We have also shown how to use Diels–Alder-initiated schemes to gain entry to double bond patterns, isomeric with those available from the DA reaction, itself.

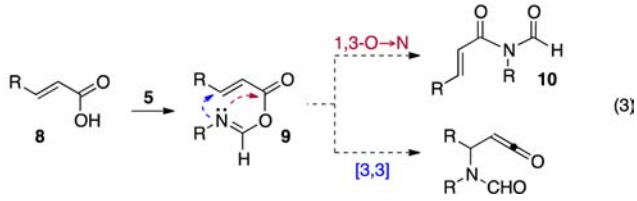
The limitation that we address in this contribution has to do with well-established (though not fully appreciated) erosion of dienophilic activity with even, seemingly, modest levels of steric hindrance, particularly at the β-carbon of the dienophile (eq 1).



For instance, α,β-unsaturated acyl-activated dienophiles (**1**, A = acid, ester, or amide) are relatively weakly reactive to thermally induced cycloaddition. When the acyl group is bound to a trisubstituted double bond, contained in a cyclene motif, DA reactivity can be quite sluggish (cf. **2**→**3**).[8−10] This is a troublesome limitation because it complicates the use of DA logic to synthesize angularly substituted *cis*-fused bicyclic motifs (cf. **3**) in a facile way.

In a totally unrelated vein, we had been investigating some important, but hitherto overlooked, chemistry of isonitriles.[11−13] During the course of those explorations, we discovered a rather general process, which we have termed two-component coupling (2CC), wherein carboxylic acids **4** react with isonitriles **5**, generally under microwave activation, to afford N-formyl amides corresponding to **7**, presumably via 1,3-O→N acyl shift of the intermediate formimidate–carboxylate mixed anhydride (FCMA, eq 2). In this connection, we wondered





whether an α,β-unsaturated acid **8**, upon reaction with an isonitrile (**5**), would give rise to **10** via the corresponding α,β-unsaturated FCMA, **9**. Not unnoticed was the possibility that **9** would not advance to **10**, but might instead undergo a formal [3,3] sigmatropic shift, leading to a ketene-bearing structure (eq 3).

The results of early probing of this question are shown in Table 1, wherein a range of α,β-unsaturated carboxylic acid substrates readily were converted to the corresponding acrylic N-formyl amides in high yield.[14] At least at present, we have not seen any positive evidence of products arising from [3,3] sigmatropic shift, although

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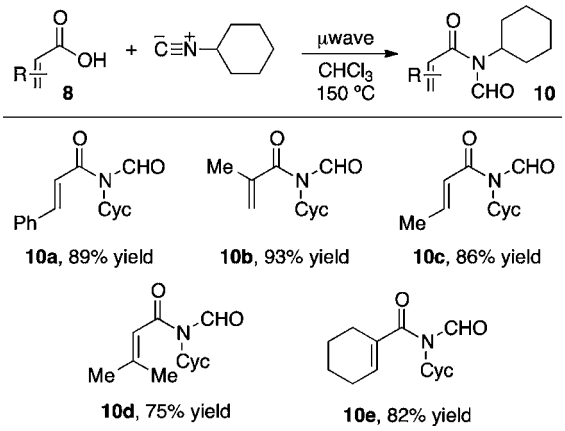
Table 1. Synthesis of Acrylic N-Formyl Amides[a]



[a]Key: Cyc = cyclohexyl.

the mode of progression of the hypothetical ketene, were it formed, is unclear.

We were now in a position to evaluate whether α,β-unsaturated N-formylamides, of the type **10**, might serve as useful new versions of α,β-acyl-activated dienophiles. In this discussion we distinguish between acyl (A, in structures **1** and **2**) and aldehydo-activated dienophiles (i.e., A = formyl). The unique opportunities in aldehyde activation, pioneered by the MacMillan school,[15−17] will be discussed below. In particular, we were hoping that the N-formylamide motif might enhance dienophilicity, thereby overcoming the type of steric hindrance problems described above. It was hoped that the electron withdrawing effect of the formyl group would enhance the dienophilicity of **10** relative to that of a simple amide. Moreover, obvious possibilities for chelation-based Lewis acid promotion presented themselves.

We began by exploring strictly thermal conditions to implement cycloaddition of **10a** with 1,3-cyclohexadiene (Table 2).[18]

Table 2. Diels-Alder Reactions[a]

entry	dienophile	catalyst	temp.	time (h)	yield (%)
1	**10a**, R = CHO	none	reflux[b]	12	30
2	**11**, R = H	none	120 °C[b]	24	0
3	**10a**, R = CHO	Et_2AlCl (2.5 equiv)	23 °C[c]	4	70
4	**11**, R = H	Et_2AlCl (2.5 equiv)	23 °C[c]	24	0

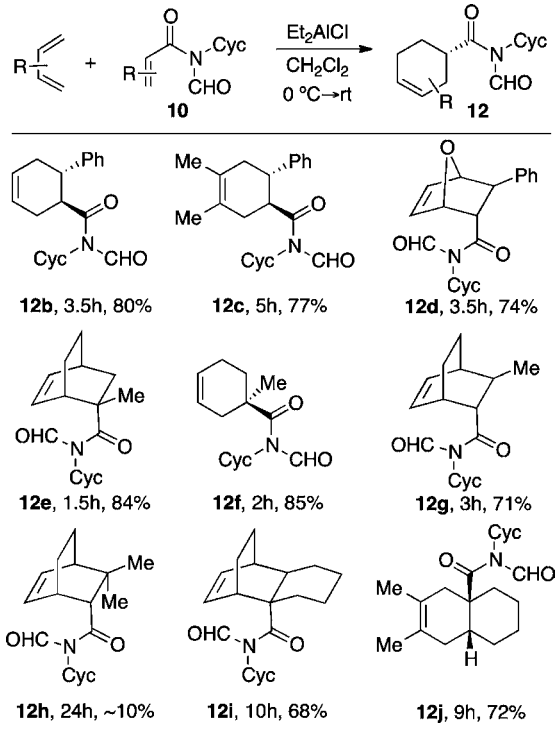
[a] CF_3CH_2OH, rt→reflux. [b]toluene, 120 °C. [c]CH_2Cl_2, o→23 °C 3 eq. of cyclohexadience were used in these studies.

For these thermal runs, we used trifluoroethanol as the solvent. In recent work in our laboratory, use of this solvent served to lower the temperature requirement for uncatalyzed cycloaddition, possibly due to reactivity enhancing interactions with the dienophile activators.[6] After 12 h at reflux, ∼30% of **10a** had undergone cycloaddition.[19] While this is far from impressive, we noted that the corresponding N-deformylated compound, **11**, upon attempted cycloaddition with the same diene, gave no observable Diels−Alder product (entry 2).

Happily, cycloaddition was nicely promoted by Et_2AlCl.[20] Thus, treatment of 1,3-cyclohexadiene and dienophile **10a** with 2.5 equiv of Et_2AlCl at room temperature afforded the DA adduct, **12a** in 70% yield and greater than 30:1 endo selectivity (entry 3).[21] An excess of Lewis acid was used in these reactions in order to ensure bidentate coordination of the imide. As found by the Evans laboratory in their investigations of the oxazolidinones,[22] we observed prohibitively slow reaction when substoichiometric amounts of Lewis acid were used. The efficiency of this transformation is of particular note, as both cinnamates and 1,3-cyclohexadiene are generally relatively unreactive partners in DA reactions.[23] In order to confirm that the high reactivity, in this case, arose from the presence of the *imide* functionality, a control experiment was performed. Thus, **10a** was deformylated, in the presence of ammonia, to generate amide **11**. As expected,[24] **11** did not undergo DA cycloaddition with 1,3-cyclohexadiene under Lewis acid conditions (entry 4).

Having defined effective conditions to achieve DA reaction in the cinnamate case, we next examined their applicability to other cases. As outlined in Table 3, dienophile **10a** undergoes

Table 3. Scope studies



[a]Three equivalents of diene was used in these reactions. endo:exo **12e** = 4:1; **12d** = 25:1, **12g** = 20:1, **12i** = 20:1.

cycloaddition with a range of diene coupling partners to produce adducts **12b−12d** in high yield. Notably, the α-substituted methacryl *N*-formyl amide, **10b**, also served as a productive coupling partner, providing cycloadducts **12e** and **12f** in high yield and generally high stereoselectivity. The relatively modest endo selectivity (4:1) observed in the particular case of the formation of **12e** is not surprising, given the known propensity of methacryl dienophiles to undergo competitive exo cycloaddition.[25] Happily, a β-substituent is nicely tolerated (see formation of **12g**). Not surprisingly, the challenging β,β-disubstituted dienophile, **10d**, failed to provide DA adduct after 12 h at room temperature.[26] Upon warming to 40 °C and stirring for an

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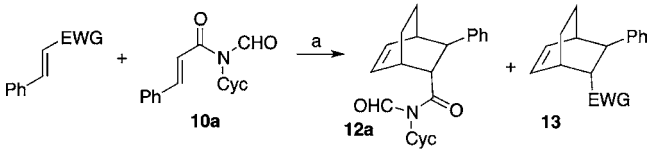
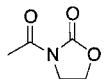
additional 6 h, ~10% of product **12h** was detected. Finally, we examined the reactivity of 1-cyclohexene-1-*N*-formyl amide **10e**. In the context of DA chemistry, the analogous 1-cyclohexenecarboxylate is a highly sluggish dienophile.[27] In contrast, the N-formyl amide-activated dienophile, **10e**, smoothly undergoes Et_2AlCl-mediated cycloaddition with both cyclohexadiene and 2,3-dimethyl-1,3-butadiene to generate adducts **12i** and **12j**, respectively.[28]

Having demonstrated that α,β-unsaturated *N*-formyl amides, under Lewis acid promotion, provide exploitable reactivity in DA chemistry, we thought it of interest to compare the dienophilicity of systems such as **10** with conventional dienophilic activators that have enjoyed long-term usage. For this purpose, we conducted a series of experiments, wherein an *N*-formyl amide-activated dienophile competes with conventional acyl activators in the same reaction flask. We also compared the *N*-formyl amide with its corresponding aldehyde.

As seen in Table 4, the dienophilicity of the *N*-formyl amide **10** totally dominated the course of the cycloaddition relative to

Table 4. Diels-Alder Competition Studies



entry	–EWG	yield (**12a**)	yield (**13**)
1	$-CO_2Me$	68%	0%
2	$-CO_2H$	63%	0%
3	–CONHCyc	68%	0%
4	–CHO	65%	5%
5		40%	40%

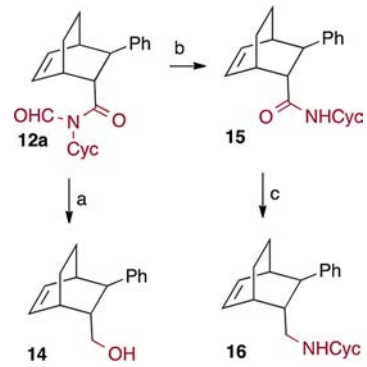
[a]2.5 equiv of Et_2AlCl; 1 equiv of cyclohexadiene, CH_2Cl_2; 3 h; 0 °C→rt.

potential competition from ester-, acid-, and amide-activated cinnamates (entries 1–3). In the monocarbonyl series, the only discernible competition (~1:13) arose from *trans*-cinnamaldehyde (entry 4). We also note that, in contrast to the aldehyde, which provides an endo:exo mixture, the corresponding reaction with **10a** appears to afford only the endo diastereomer. In a direct competition experiment, the *N*-formyl amide **10a** was found to possess levels of reactivity equivalent to the well-established oxazolidinone-activated dienophile (entry 5).[29]

It was important to address questions as to the manipulability of the N-formyl amide in the DA product. The N-formyl amide motif may be readily converted to a range of traditional functional groups. For example, the facile three-step conversion of cycloadduct **12a** to alcohol **14** and amide **15** is shown in Scheme 1.[30] The amide can be further reduced to amine **16.**

We next envisioned expanding this technology to enable the rapid synthesis of complex polycyclic systems (cf. **20** and **24**, Figure 1). This would be accomplished by coupling of "value added" isonitrile and carboxylic acid substrates, followed by intramolecular Diels–Alder (IMDA) cycloaddition. In one potential application, installation of the diene coupling partner on the isonitrile functionality (**17**) would serve to generate, following 2CC with an α,β-unsaturated acid, a potential IMDA substrate, **19**. Subsequent Lewis acid-mediated cyclization would provide access to bicyclic systems of the type **20**. Alternatively, we field

Scheme 1. Functionalization of N-Formyl Amides Adducts[a]



[a]Key: (a) (i) $NaBH_4$, MeOH (ii) Et_3SiH, TFA, CH_2Cl_2 (iii) LDA, BH_3NH_3, THF. 74% over three steps (b) NH_3, MeOH, >95%. (c) LAH, Et_2O, 90%.

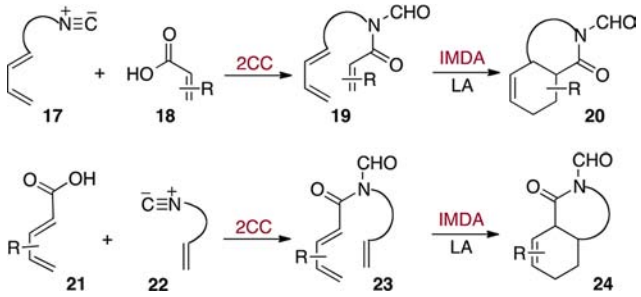
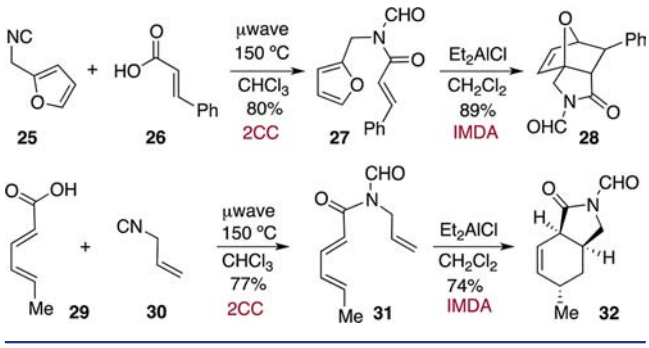


Figure 1. IMDA.

tested the possibility that the acyl group could be attached to the diene (cf. **21**), while the isonitrile moiety might bear the dienophilic element (**22**). In this setting, the N-formyl amide would serve to activate the diene of **23**, thereby promoting an inverse-demand type IMDA cycloaddition to yield a complementary set of cycloadducts (cf. **24**).[31–33]

We first examined the feasibility of the normal demand IMDA. Thus, compound **25** was prepared from the commercially available primary amine.[34] Subsequent 2CC with **26** provided IMDA substrate, **27** (Scheme 2). Notably, formation of small

Scheme 2. IMDA with Acrylic N-Formyl Amides



amounts of IMDA cyclization adduct was already observed following the microwave irradiation of the 2CC reaction. Upon treatment with Et_2AlCl, the substrate readily underwent cyclization to furnish tricyclic adduct **28** as a single diastereomer. We next investigated the feasibility of the proposed inverse demand IMDA sequence. Intermediate **31** was thus readily prepared through 2CC of acid **29** and isonitrile **30**.[35] Subsequent Et_2AlCl-mediated

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cyclization delivered **32** as the main product in good yield as a single observable diastereomer.

During the course of these studies we were certainly sensitive to the opportunities offered by the oxazolidinone type of dienophilic activation pioneered by Evans and associates.[22] Inherent in Evans' results was the recognition that activation by imide-based dienophiles surpasses that of the usual acyl type activators. Moreover, the very elegant adaption of such auxiliaries to the attainment of high levels of diastereo- and enantioselection has been of great utility. Also compelling has been the application of organocatalysis, resulting in major enhancement of the dienophilic propensities of α,β-unsaturated aldehydes and ketones, described by MacMillan.[15−17] Here also, high levels of enantioselection, arising via diastereo-differentiated transition states, magnified the power of the catalysis. While one can imagine corresponding opportunities for high enantioselection with type **10** dienophiles, we have, presently, not achieved acceptable levels of induction. Rather, the value of the chemistry described above lies in its ability to merge complex functionalities in putative diene and dienophile sectors, by the 2CC reaction, thereby enhancing the level of molecular complexity available by this logic, while providing ample "machinery" for conducting the projected DA cycloaddition. The critical part of the DA-enabling machinery is the N-formyl group. Following DA cycloaddition (either inter- or intramolecular see Table 3 and Scheme 2, respectively), the N-formyl group, if extraneous to the target, is quickly discharged, leaving the rest of the complexity-enhancing functionality *in place*. Ongoing research is directed to building upon the paradigm, captured in Figure 2, while also seeking to gain high

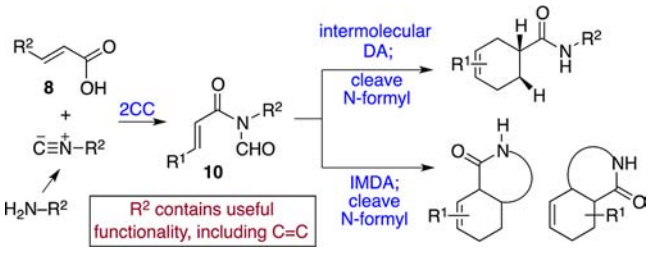

Figure 2.

enantiocontrol through appropriate catalytic guidance via diastereo-differentiating transition states. Results will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedures, including spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

s-danishefsky@ski.mskcc.org

Notes

The authors declare no competing financial interest.

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(19) The bulk of the recovered dienophile had not reacted.
(20) The reaction was quenched before complete consumption of the starting materials to avoid formation of other products.
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(28) The reactions described in Tables 2 and 3 were performed on 0.1 mmol scale. We have demonstrated the preparatory value of this chemistry in the context of the cycloaddition of 650 mg (2.5 mmol) of **10a** with cyclohexadiene to afford a 72% yield of **12a**. The isolated yield

of this large-scale reaction is similar to that obtained on 0.1 mmol scale (see Table 2). See Supporting Information for details.
(29) On the advice of one reviewer, we also performed the competition experiments in Table 4 with 5 equiv of Et_2AlCl and observed no change in product distribution.
(30) We note that to accomplish the transformation to **14**, it was necessary to convert N-formyl to N-methyl.
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